UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/839,884	04/20/2001	Rudolf Hans Aebersold	64-98A	4321

23713 7590 05/23/2002

GREENLEE WINNER AND SULLIVAN P C
5370 MANHATTAN CIRCLE
SUITE 201
BOULDER, CO 80303

EXAMINER	
GABEL, GAILENE	
ART UNIT	PAPER NUMBER
1641	6

DATE MAILED: 05/23/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/839,884	AEBERSOLD ET AL.	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on th cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 April 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims Under Examination

1. Claims 1-28 are pending and under examination.

Drawings

2. This application has been filed with informal drawings which are acceptable for examination purposes only. Correction is required.

Specification

3. The following guidelines illustrate the preferred layout and content for patent applications. These guidelines are suggested for the applicant's use.

(a) Title of the Invention.
(b) Cross-References to Related Applications.
(c) Statement Regarding Federally Sponsored Research or Development.
(d) Reference to a "Microfiche Appendix" (see 37 CFR 1.96).
(e) Background of the Invention.
    1. Field of the Invention.
    2. Description of the Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(f) Brief Summary of the Invention.
(g) Brief Description of the Several Views of the Drawing(s).
(h) Detailed Description of the Invention.
(i) Claim or Claims (commencing on a separate sheet).
(j) Abstract of the Disclosure (commencing on a separate sheet).
(k) Drawings.
(l) Sequence Listing (see 37 CFR 1.821-1.825).

Specifically, a "Brief Description of the Several Views of the Drawing(s)" and "Detailed Description of the Invention" are missing in the specification. Correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite in failing to recite a positive limitation in the claim in reciting, "can be differentially labeled with stable isotopes".

In claim 1, the second occurrence of "that selectively" should be deleted to remove redundancy.

Regarding claim 1, the phrase "certain protein functional groups" renders the claim indefinite because the claim includes elements not actually disclosed (those encompassed by "certain ... groups"), thereby rendering the scope of the claims unascertainable.

Claim 6 has improper antecedent basis problem in reciting, "a affinity label".

Claim 6 has improper antecedent basis problem in reciting, "a protein reactive group".

Claim 6 has improper antecedent basis problem in reciting, "a linker group".

Claim 6 recites improper Markush language in reciting, "selected from ... or (CH2)q;".

Claim 8 recites improper Markush language in reciting, "selected from ... or an oligohistidine".

Claim 15 lacks antecedent support in reciting, "the deficiency".

Claim 16 lacks antecedent support in reciting, "the deficiency".

Information Disclosure Statement

5. The information disclosure statement filed 1/14/02 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-7, 9-10, 12-16, 18-20 and 22-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sigler et al. (US 4,798,795) in view of Duncan et al. (Analytical Chemistry, March 1998).

Sigler et al. disclose an affinity tagged protein reactive reagent for use in isolating proteins in a sample mixture via affinity chromatography. The reagent comprises a biotin (affinity label), a disulfide linker group, and a protein reactive group, i.e. aryl thiol (dithiopyridyl) or N-hydroxysuccinimide ester, that selectively reacts with protein functional groups so that in use, the reagent reacts with a thiol, such as a protein thiol, to release pyridine-2-thione and yield a biotin-dithio-linked protein (see columns 1, 2, and 3). The protein reactive reagent is captured into an avidin affinity matrix (capture reagent) which selectively binds biotin then released by disrupting the interaction between the biotin component of the reagent and the avidin affinity matrix (recovered by reduction of the disulfide bonds) (see column 5, lines 35-54). The progress of a reaction is monitored using spectrophotometric measurements of a chromogenic product.

Sigler et al. fail to teach differentially and isotopically labeling the proteins or peptides using stable isotopes. Sigler et al. also differ in failing to teach detecting and identifying released affinity tagged components using mass spectrometry.

Duncan et al. teach analyzing peptides and proteins on the femtomole scale using isotope dilution chromatography and mass spectrometry (see Abstract). Duncan further teach adding to the sample mixtures, stable isotope labeled amino acids forms for use as internal standards (see page 891, columns 1 and 2). Both components in the mixture are converted to electron capturing derivatives then injected into a chromatograph interfaced with a mass spectrometer - GC/MS system (see page 893, column 1). Thereafter, the absolute amounts of the amino acids relative to the internal standard is measured and calculated (see Abstract). According to Duncan et al., using stable isotope labeled standards for each amino acids during hydrolysis, derivatization, and GC/MS injection, reduces the need of correction for losses of specific protein components, thereby providing accurate and sensitive quantification of proteins and peptides (see page 895, column 1 and page 890, column 2).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate stable isotopes such as taught by Duncan into the reagent taught by Sigler because Duncan specifically used the stable isotope to label internal standard proteins/peptides to monitor activity and quantitate concentrations of proteins/peptides in a chromatographic/mass spectrometric system. One of ordinary skill in the art at the time of the instant invention would have been motivated to incorporate the teaching of Duncan in differential isotope labeling of proteins/peptides

into the reagent taught by Sigler because Duncan specifically taught the advantage of stable isotope labeled standards in protein/peptide quantitation methods in reducing losses protein components and providing accuracy an sensitivity in such methods.

7. Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sigler et al. (US 4,798,795) in view of Duncan et al. (Analytical Chemistry, 3/1998) as applied to claims 1-20 and 22-28 above, and further in view of Allen et al. (US 5,438,017).

Sigler et al. and Duncan et al. have been discussed supra. Sigler et al. and Duncan et al. differ in failing to teach substituting a heavy isotope for differentially labeling one or more atoms in the reagent.

Allen et al. disclose addition of internal standard into samples wherein the internal standards of proteins or peptides are isotopically labeled with heavy (metal) isotopes such as deuterium (deuterated homocysteine or deuterated methylmalonic acid) (see columns 5 and 6). Allen et al disclose using heavy metal isotopes in a method for analyzing proteins and peptides (sulfydryl amino acid and methylmalonic acid) using a GC/MS system.

One of ordinary skill in the art at the time of the instant invention would have reasonable expectation of success in substituting a heavy metal isotope label such as deuterium as taught by Allen for the stable isotope label taught by Duncan in the reagent of Sigler because Allen specifically taught application of heavy isotope in labeling internal protein standards, i.e. deuterium in GC/MS systems.

8. Claims 8, 11, and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sigler et al. (US 4,798,795) in view of Duncan et al. (Analytical Chemistry, 3/1998) as applied to claims 1-7, 9-10, 12-16, 18-20 and 22-28 above, and further in view of Markert-Hahn et al. (US 5,514,559).

Sigler et al. and Duncan et al. have been discussed supra. Sigler et al. and Duncan et al. differ in failing to teach a hapten, or a 1,2 diol, glutathione, maltose, nitrilotriacetic acid group, or oligohistidine as affinity label in the reagent. Sigler et al. and Duncan et al. also fail to teach iodoacetylamide groups, epoxides, an alpha-haloacyl groups, nitriles, sulfonated alkyls, aryl thiols, or maleimides as protein reactive groups (PRG) in the reagent. Finally, Sigler et al. and Duncan et al. differ in failing to teach that the PRG of the reagent is a substrate for B-galactosidase, acetyl-alpha-D-glucosaminidase, heparan sulfamidase, acetyl-CoA-alpha-D-glucosamide N-acetyltransferase or N-acetylglucosamine-6-sulfatase.

Markert-Hahn et al. disclose stable reagents comprising an affinity label, a linker, and protein reactive groups combined as immunologically active conjugates for use in binding interactions between proteins, enzymes such as beta-glucosidase, peptides such as beta-glucosidase subunits, haptens, and polymers which are covalently bound via bifunctional linkers such as those containing maleiminido group and thiol groups. Other groups suitable to bind the linkers to the coupling protein or peptide components include N-hydroxysuccinimide, amino alkyl carboxylic acids, and activated aryl ester groups. These conjugates are useful in determining immunologically and functionally

active proteins (or peptides) in immunological quantitation methods (see columns 1 and 2).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to substitute the components used as immunologically active conjugates taught by Markert-Hahn for the affinity labels and protein reactive groups in the reagent taught by Sigler as modified by Duncan, because Markert-Hahn specifically taught using different sets of conjugates that are taught in reagents used in his method to analyze and quantitate active protein mixtures. Further, the different affinity labels recited in claim 8 constitute obvious modifications of species which are routinely varied in the art and which have not been described as being critical to the practice of the invention.

9. No claims are allowed.

Remarks

10. Prior art made of record are not relied upon but considered pertinent to the applicants' disclosure:

Rothschild et al. (US 6,057,096) disclose biotin derivative containing N-hydroxysuccinimide ester group for use in linking biotin through an amide bond to proteins (see columns 6-7).

Ghazarossian et al. (US 5,614,368) disclose compounds comprising haptens bound directly or indirectly to a chromophoric group and a macromolecule-reactive group.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gail Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday to Thursday from 7:00 AM to 4:30 PM. The examiner can also be reached on alternate Fridays from 7:00 AM to 3:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (703) 308-3399. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gailene R. Gabel
Patent Examiner
Art Unit 1641

LONG V. LE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600
05/20/02